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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,818	04/26/2001	Anthony Steven Weiss	GHC11USA	8602

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,818	WEISS, ANTHONY STEVEN	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-89* is/are pending in the application.

4a) Of the above claim(s) *68-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/24/01 & 10/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 46-67, in the reply filed on 10/27/03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The examiner notes that Claim 67 was incorrectly placed in Group II due to the confusion over claim numbering. Claim 67 is presently rejoined with Group I and will be examined in this Office Action.

Status of the Claims

Claims 46-89 are pending. Claims 68-89 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 46-67 have been considered in this Office Action.

Claim Objections

Claims 50, 51, 59, 60, and 61 are objected to for the recitation of "aa". For clarity, this abbreviation should be written out as "amino acids".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-49, 52-53, 56, 58, 65, and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing the susceptibility of tropoelastin to thrombin, kallikrein, trypsin, plasmin, gelatinase B, or serum by mutating the sequences described in the Specification (see Table I for example), does not reasonably provide enablement for a method for reducing or *eliminating* the susceptibility of a tropoelastin to proteolysis by *any* protease comprising mutating *any* sub-sequence in the tropoelastin so that the susceptibility of the tropoelastin to proteolysis is reduced or *eliminated*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation would be required to characterize all of the possible protease cleavage sites in tropoelastin so that the full scope of the claimed method could be practiced with a reasonable expectation of success. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The *nature of the invention* involves the finding of potential cleavage recognition sites in the tropoelastin sequence for thrombin, kallikrein, trypsin, plasmin, gelatinase B,

and serum by digesting tropoelastin with each protease and sequencing the resulting peptide fragments.

The *breadth of the claims* is so broad as to encompass complete inhibition (elimination) of cleavage of tropoelastin by any protease by mutating any sequence in tropoelastin that "is capable of" being cleaved by a protease. The examiner notes that "sub-sequence" has been defined on page 11 of the present Specification as "a sequence which is capable of being cleaved (or in other words, digested) by a protease when tropoelastin or a tropoelastin variant is folded in a functional conformation" (p. 11, lines 8-11).

The *state of the prior art and relative skill of those in the art* is such that those of skill in the art were aware that serine proteases were involved in the processing of tropoelastase. For example, Mecham et al. (references AY, AZ, and AAR of IDS filed May 24, 2001) describe an enzyme that cleaves tropoelastin with a trypsin like specificity. Hayashi et al. (ref. AW) of IDS filed May 24, 2001) describe a 45 kD tropoelastin degradation product processed by a metal protease. And, Romero et al. (ref. AAT of IDS filed May 24, 2001) teaches that calcium dependent proteases, kallikrein, trypsin, and elastase are effective in the degradation of tropoelastin but that the major source of proteolytic activity in serum was not clear. There is no teaching or suggestion in the art of mutating protease cleavage sites contained in tropoelastin in order to decrease susceptibility to protease cleavage. In addition, there are innumerable proteases with unique sequence specificities such that any protein can be completely degraded with a combination of non-specific proteases (for example,

pronase, a mixture of non-specific proteases from S. griseus is often used to give complete proteolysis; see Voet and Voet, Biochemistry N.Y., John Wiley & Sons, 1990, p. 116.

The Specification provides *guidance and examples* of resulting peptide sequences after tropoelastin digestion with thrombin, kallikrein, trypsin, plasmin, gelatinase B, and serum (see Table I). The Specification does not provide any examples of a specific tropoelastin wherein a protease cleavage is reduced or eliminated by mutation of a protease cleavage site. The Specification and claims do provide guidance as to what specific protease cleavage sequences and which amino acids within those sequences could be mutated. For example, the specification and claims indicate that susceptibility of tropoelastin to thrombin, kallikrein, or serum cleavage could be reduced by mutating the sequence RAAAG at position 515 in the human tropoelastin sequence (see Table I and claims) and more specifically by replacing arginine with alanine. In addition, claim 54 indicates that tropoelastin susceptibility to thrombin cleavage could be reduced by mutating the amino acid sequence of SEQ ID NOs: 8 or 9 in the tropoelastin sequence. Claim 55 indicates that tropoelastin susceptibility to plasmin can be reduced by mutation of the sequences of SEQ ID NO:11 or 12 in the tropoelastin sequence. Claim 57 indicates that tropoelastin susceptibility to kallikrein cleavage can be reduced by mutation of the sequences of SEQ ID NOs: 9 or 10 within the tropoelastin sequence. Claim 59 indicates that tropoelastin susceptibility to metalloproteinase cleavage can be reduced by mutating the sequence of amino acids 1-5 of SEQ ID NO: 13 or any one of SEQ ID NOs: 45-70

within the tropoelastin sequence. Claim 66 indicates that the susceptibility of tropoelastin to gelatinase A or B cleavage can be reduced by mutating the amino acid sequence of SEQ ID NO: 13 in the tropoelastin sequence. Thus, given the examples summarized in Table I and the guidance in the Specification, these methods involving mutating specific sequence to result in reduced susceptibility to specific protease cleavage are considered enabled.

Given the lack of knowledge about tropoelastin susceptibility to proteases other than those tested in the present Specification, it would be highly unpredictable as to what sequences other than those described in the Specification could be mutated to reduce protease susceptibility.

Therefore, for the reasons given above, the quantity of experimentation required to practice the claimed method commensurate in scope with the claims is considered undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of all the proteases that cleave tropoelastin and the cleavage recognition sites in order to eliminate or reduce the susceptibility of tropoelastin to proteolysis. It is this additional characterization constitutes undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49 and 50 are rejected because they improperly depend from themselves and therefore are unclear as to what method is being referred. Claims 51-57 are also rejected since they depend from Claims 49 and 50 yet do not correct their deficiencies.

Claims 49, 54, 55, 56, 58, and 65 are indefinite for the recitation of "capable of" as this is a latent term which implies that there are times that the sub-sequence cannot be digested by the given protease. It is suggested that the claim be rewritten as, for example, "wherein the sequence is cleaved by thrombin". Claims 50-53, 57, 59-64, and 66 are rejected since they depend from these rejected claims yet do not correct their deficiencies.

Claims 46-67 are indefinite as to the metes and bounds of "sub-sequence". The term sub-sequence has been defined as "a sequence which is capable of being cleaved (or in other words, digested) by a protease when tropoelastin or a tropoelastin variant is folded in a functional conformation" (p. 11, lines 8-11). The Specification further states that the "sub-sequence correspond to the amino acid sequences in the regions of tropoelastin which are susceptible to proteolysis" (p. 11, lines 14-16). However, this definition does not place a limit on the sequence length. How much of the protease cleavage site is considered a "sub-sequence". A protease cleaves between two amino acids. Therefore, does the "sub-sequence" contain only those two amino acids or may

it contain the full-length tropoelastin sequence? Claims 50 and 59 further confuse the matter because they indicate that the sub-sequence *includes* specific sequences--suggesting that the recited sequence does not make up the entire sub-sequence. Clarification is required.

Conclusions

No Claims are allowable.

The prior art of record does not teach or suggest mutating the specific sequences provided in the Specification in order to reduce susceptibility of tropoelastin to cleavage by the corresponding specific proteases. The examiner suggests the following claim as an example of one which would overcome the rejections above:

A method for reducing the susceptibility of tropoelastin to kallikrein cleavage comprising mutating any of the residues 517-523 of SEQ ID NO:4 so that the susceptibility of the tropoelastin to kallikrein cleavage is reduced.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
December 7, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER